Neue Entwicklungen in der experimentellen Pharmakopsychotherapie

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Studie zeigt: Antidepressiva wirken kaum besser als Placebo.

BMJ Open
Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis

Klaus Munkholm, Asger Sand Paludan-Müller, Kim Boesen

ABSTRACT
To investigate whether the conclusion of a recent systematic review and network meta-analysis (Cipriani et al) that antidepressants are more efficacious than placebo for adult depression was supported by the evidence.

Design: Reanalysis of a systematic review, with meta-analyses.

Data sources: 522 trials (116,477 participants) as reported in the systematic review by Cipriani et al and clinical study reports for 19 of these trials.

Analysis: We used the Cochrane Handbook's risk of bias tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the risk of bias and the certainty of evidence, respectively. The impact of several study characteristics and publication status was estimated using pairwise subgroup meta-analyses.

Results: Several methodological limitations in the evidence base of antidepressants were either unrecognised or underestimated in the systematic review by Cipriani et al. The effect size for antidepressants versus placebo on investigator-rated depression symptom scales was higher in trials with a “placebo run-in” study design compared with trials without a placebo run-in design (p=0.056). The effect size of antidepressants was higher in published trials compared with unpublished trials (p=0.0001). The outcome data reported by Cipriani et al...

Strengths and limitations of this study

- Empirical evidence was provided showing how many biases and methodological limitations in the evidence base for antidepressants for depression affect the apparent effect size for antidepressants.
- For the first time, the impact of the “placebo run-in” study design on the apparent effect size for antidepressants compared with placebo was estimated.
- We reported the effect estimate of antidepressants compared with placebo as a mean difference on the investigator-rated Hamilton depression rating scale to provide an outcome measure that can be easily interpreted by patients and clinicians.
- When possible, we compared the data reported by Cipriani et al on the outcomes of total dropouts and dropouts due to adverse events with the clinical study reports that we have previously obtained from the European Medicines Agency.
- Our analyses relied on the data reported in the systematic review by Cipriani et al and we did not perform a separate literature search and data extraction; given the methodological limitations we have identified, a reliable assessment would need to be based on clinical study reports and individual patient data.
The Psychedelic Renaissance

High hopes

Psychedelic drugs fell from grace in the 1960s. Now, scientists are rediscovering them as potential treatments for a range of illnesses

By Kai Kupferschmidt
High hopes

Psychedelic drugs fell from grace in the 1960s. Now, scientists are rediscovering them as potential treatments for a range of illnesses.
The Psychedelic Renaissance
The Concept of Pharmacopsychotherapy

Pharmaceutical

Psychopharmacological agents:
- Psilocybin, MDMA, DMT, LSD: empathy, attachment, learning, fear extinction, emotion regulation
- D-Cycloserin (NMDA-R-agonist): fear extinction in behavioral exposure therapy (phobia, panic, OCD)
- Oxytocin: support positive social experiences, trust, and relationship-focused processes in psychotherapy

Psychotherapy

Central Nervous System

Psychological Wellbeing
The Concept of Pharmacopsychotherapy

**Psilocybin, MDMA, DMT, LSD:** empathy, attachment, learning, fear extinction, emotion regulation

**Limitations:**
- limited generalizability due to small samples (mostly young & educated)
- lack of placebo-control in feasibility/pilot studies
- difficulty with blinding, expectancy bias
- drop-outs bias positive outcomes
- lack of systematized psychotherapeutic methods
- lack of long-term follow-up
Special permission by the Swiss Federal Office for Public Health (FOPH) to psychiatrists of the Swiss Medical Society for Psycholytic Therapy (1988-1993)

- **N=171 patients, 125 mg of MDMA and/or low to high doses of LSD (100-400 ug)**
- **group therapy setting** supported by music and guidance
- 70 sessions of psychotherapy interleaved with 7 psycholytic sessions over 3 years (average)
- **Personality disorders (38%), adjustment disorders (25%), affective disorders (25%), eating disorders (6%)**
- **Good (65%), slight (26%) improvement vs. no change (4%), fluctuations (3%) and worsening (2%)**
Special permission by the Swiss Federal Office for Public Health (FOPH) to psychiatrists of the Swiss Medical Society for Psycholytic Therapy (1988-1993)

- No proof of efficacy - due to limitations:
  - retrospective data evaluation (follow-up questionnaires)
  - lack of systematic study design
  - lack of randomized control / placebo group
A randomized, controlled pilot study of MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD)

Peter Oehen¹, Rafael Traber², Verena Widmer³ and Ulrich Schnyder³

LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects

Peter Gasser¹, Katharina Kirchner² and Torsten Passie¹

![Graphs and diagrams illustrating changes in anxiety levels before and after treatment with MDMA and LSD.](image-url)
## History of Psychedelic Therapy (CH)

### Table 1. Psychological effects of MDMA in the context of psychotherapy.

<table>
<thead>
<tr>
<th>Category</th>
<th>MDMA-induced state</th>
<th>Psychotherapeutic implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood/Affect</td>
<td>Mild euphoria</td>
<td>Positive and fearless emotional state of well-being</td>
</tr>
<tr>
<td></td>
<td>Anxiety and fear ↓</td>
<td>Emotional avoidance ↓</td>
</tr>
<tr>
<td></td>
<td>Enhanced perception of and intensified feelings</td>
<td>Tolerance and processing of difficult emotions (“window of tolerance”) ↑</td>
</tr>
<tr>
<td></td>
<td>Affect tolerance ↑</td>
<td></td>
</tr>
<tr>
<td>Cognition/ Memory</td>
<td>More imaginative and associative</td>
<td>Recall of relevant traumatic memories ↑</td>
</tr>
<tr>
<td></td>
<td>Contemplativeness ↑</td>
<td>Prolonged spontaneous exposure to traumatic memories</td>
</tr>
<tr>
<td></td>
<td>Recall and tolerance of traumatic memories ↑</td>
<td>Cognitive restructuring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“simulation of alternative behavior”</td>
</tr>
<tr>
<td>Attachment/ Interpersonal Behavior</td>
<td>Social fears and defensiveness ↓</td>
<td>Improvement of therapeutic alliance</td>
</tr>
<tr>
<td></td>
<td>Social approach behavior ↑ with empathy, openness, trust, feelings of being connected to others ↑</td>
<td>Rebuilding of trusting relationships</td>
</tr>
<tr>
<td></td>
<td>Cuddling and need for touch ↑</td>
<td>Defensiveness and isolation ↓</td>
</tr>
<tr>
<td>Self</td>
<td>Self-esteem ↑</td>
<td>Grounding/centering ↑</td>
</tr>
<tr>
<td></td>
<td>Self-acceptance ↑</td>
<td>Consolidation of self ↑</td>
</tr>
<tr>
<td>Body</td>
<td>Release of muscular tension</td>
<td>Release of tension and reduction of somatic symptoms</td>
</tr>
<tr>
<td></td>
<td>Analgesia</td>
<td>Positive body image</td>
</tr>
<tr>
<td></td>
<td>Sensuality ↑</td>
<td></td>
</tr>
</tbody>
</table>

MDMA: 3,4-methylenedioxymethamphetamine

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Oehen et al.
J Psychopharm, 2013
Compassionate Use (CH)

- Since 2012 special permissions were issued for compassionate use with cannabis (~14’000 patients) and since 2014 for controlled illicit substances (LSD, MDMA, psilocybin; n~50 patients)

Increasing number of patients treated with cannabis within the compassionate use framework
Compassionate Use (CH)

«Unlicensed» medical use of prohibited narcotics outside of clinical trials

- **Requirements for the application to the FOPH**
  - only authorized doctors in Switzerland can submit an application for patients with Swiss domicile
  - patient information including diagnosis and indication for treatment, and written informed consent
  - justification for the desired treatment (medical history, previous therapies, clinical course...)
  - drug and intervention (e.g., cannabis, psilocybin, LSD, MDMA)
  - dosage, duration of treatment, source of supply, assumption of the treatment costs
  - interim report on the course of the treatment (duration of regular permit: 1 year)
  - at the end of treatment and in case of prolongation or termination (death, unsatisfactory effect, etc.)

<table>
<thead>
<tr>
<th>Compassionate use (approved by FOPH)</th>
<th>Experimental therapy (approved by ethics as research)</th>
</tr>
</thead>
<tbody>
<tr>
<td>primarily initiated based on individual patient</td>
<td>primarily initiated by investigator for a group of patients</td>
</tr>
<tr>
<td>no scientific question</td>
<td>scientific question</td>
</tr>
<tr>
<td>no systematic approach</td>
<td>standardized procedures (intervention, data collection)</td>
</tr>
<tr>
<td></td>
<td>additional diagnostics without individual need for patient</td>
</tr>
</tbody>
</table>
Ongoing clinical phase II and III studies with psilocybin, LSD, and MDMA (source: clinicaltrials.gov)

- University of Zurich: Clinical, Neurocognitive, and Emotional Effects of Psilocybin in Depressed Patients
- University of Zurich: Clinical and Mechanistic Effects of Psilocybin in Alcohol Addicted Patients
- Imperial College London: Psilocybin vs Escitalopram for Major Depressive Disorder: Comparative Mechanisms
- Usona Institute: A Study of Psilocybin for Major Depressive Disorder (MDD)
- COMPASS Pathways: The Safety and Efficacy of Psilocybin in Participants With Treatment Resistant Depression
- University of Basel: LSD Treatment in Persons Suffering From Anxiety Symptoms in Severe Somatic Diseases or in Psychiatric Anxiety Disorders
- University of Basel: LSD Therapy for Persons Suffering From Major Depression
- University of Basel: LSD as Treatment for Cluster Headache
- MAPS: A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD
- MAPS Europe: Open Label Multi-Site Study of Safety and Effects of MDMA-assisted Psychotherapy for Treatment of PTSD
Clinical Trials with Psychedelics

JAMA Psychiatry | Original Investigation

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder
A Randomized Clinical Trial

Alan K. Davis, PhD; Frederick S. Barrett, PhD; Darrick G. May, MD; Mary P. Cosimano, MSW; Nathan D. Sepeda, BS; Matthew W. Johnson, PhD; Patrick H. Finan, PhD; Roland R. Griffiths, PhD

Figure 2. Study Timeline From Baseline Assessment and Screening to the 4-Week Postsession-2 Follow-up Visit
Clinical Trials with Psychedelics

JAMA Psychiatry | Original Investigation

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder
A Randomized Clinical Trial

Figure 3. Comparison of GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups

Data points are presented as mean (SD). In the immediate treatment group (n = 13), weeks 5 and 8 correspond to weeks 1 and 4 after the psilocybin session 2. In the delayed treatment group (n = 11), weeks 5 and 8 are prepsilocybin assessments obtained during the delay period. Effect sizes (Cohen d with 95% CI) and P values reflect the results of a 2-sample t test between the 2 groups at week 5 (Cohen d = 2.2; 95% CI, 1.4-3.0; P < .001) and week 8 (Cohen d = 2.6; 95% CI, 1.7-3.6; P < .001).

Figure 4. Decrease in the GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores at Week 1 and Week 4 Postsession-2 Follow-up in the Overall Treatment Sample

The mean (SD) GRID-HAMD score was 22.8 (3.9) at baseline, 8.7 (7.6) at week 1, and 8.9 (7.4) at week 4. Effect sizes (Cohen d with 95% CI) and P values reflect the results of a paired sample t test that compared scores between baseline and week 1 (Cohen d = 3.6; 95% CI, 2.2-5.0; P < .001) and week 4 postsession-2 follow-up (Cohen d = 3.6; 95% CI, 2.2-4.9; P < .001).
Wahrnehmungsveränderungen:
- Intensivierung der Sinneswahrnehmung (Reizoffenheit)
- Pseudohalluzinationen (z.B. geometrische Formen, Farben, Muster)
- audio-visuelle Verzerrungen, Synästhesien und Illusionen
- ästhetische Wahrnehmung

Psychische Effekte:
- Intensivierung von Emotionen mit Affektlabilität (Euphorie, Angst, etc.)
- Veränderte Raum/Zeit-Wahrnehmung, Derealisation, Depersonalisation, Dissoziation
- Verändertes Denken (Kreativität, Bedeutungserleben, Konzentrationsschwierigkeiten)
- Traumähnliche Visionen, introspektive Versenkung, ekstatische Bewusstseinserweiterung

Körperliche Effekte:
- Blutdruck- und Pulsanstieg, Palpitationen, Schwindel
- Schwitzen, Kälteschauer
- Mydriasis, Verschwommensehen
- Nausea, Erbrechen (v.a. pflanzliche Halluzinogene)
- Koordinationsstörungen, Unruhe, Tremor, Krämpfe, Katatonie
- Entspannung, Schlaflosigkeit oder Schlafstörung
Molecular Structure of Psychedelics

Reiff et al.
Am J Psych, 2020

Vollenweider
Dialogues Clin Neurosci, 2001

Selected abbreviations and acronyms

- DOI: 3,4-Methylenedioxymethamphetamine
- LSD: Lysergic acid diethylamide
- 5-HT: Serotonin
- DA: Dopamine
- CSTC: Cortico-striato-thalamo-cortical
- CSPT: Cortico-striato-pallido-thalamic
- AED: Amphetamine-Derivate
- PPI: Prepulse inhibition
- VR: Visionary restructuralization
- DA: Dopamine
- NMDA: N-Methyl-D-aspartate

Pharmacological aspects

Psychedelic hallucinogens can be classified by either the neuronal basis of drug-induced ASC and its relation to the startle reflex. Furthermore, receptor mechanisms of hallucinogenic and related drugs have been investigated by exploring the effects of specific receptor agonists and antagonists. A second class of drugs with hallucinogenic properties often share psychedelic effects of serotonergic hallucinogens downstream of a common neurotransmitter system or downstream of a common downstream of a common neurotransmitter system. Finally, a third class of drugs, the so-called "entactogens," produce effects that are closely related structurally to hallucinogenic arylocyclohexylamines such as mescaline and 2,5-dimethoxy-4-iodoamphetamine. Such drugs include PCP and ketamine. These agents primarily act upon 5-HT receptors and partly upon the dopamine (DA) receptors.

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### Differential Effects of Psychedelics

**TABLE 1. Primary pharmacological mechanisms of action of the psychedelic compounds and their cognitive, perceptual, emotional, and social relatedness effects**

<table>
<thead>
<tr>
<th>Class and Compound</th>
<th>Primary Mechanism of Action</th>
<th>Cognition</th>
<th>Perception</th>
<th>Negative Emotions</th>
<th>Positive Emotions</th>
<th>Social Relatedness</th>
<th>Other Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic psychedelics</strong></td>
<td></td>
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<tr>
<td>LSD, psilocybin, and ayahuasca (DMT)</td>
<td>Serotonin 5-HT&lt;sub&gt;2A&lt;/sub&gt; and 5-HT&lt;sub&gt;2C&lt;/sub&gt; receptor agonist</td>
<td>Increased cognitive flexibility (53), creative thinking (51), and insightfulness (52); distractibility and disorganized behavior (49, 51, 53, 62)</td>
<td>Changes in visual perception (51, 53); mystical experiences (6, 12, 34, 52); paranoia (53); hallucinations, depersonalization, derealization (51, 62, 69)</td>
<td>Anxiety (29, 51, 69); labile mood with anxiety (34)</td>
<td>Increase in well-being and life satisfaction (70); positive mood (60, 71) or blissful state (52, 53, 69)</td>
<td>Enhanced empathy (50); prosocial attitudes and behaviors (34); openness and trust (69)</td>
<td>Mescaline</td>
</tr>
<tr>
<td><strong>Entactogens</strong></td>
<td></td>
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<tr>
<td>MDMA</td>
<td>Serotonin 5-HT&lt;sub&gt;2A&lt;/sub&gt; agonist; mixed serotonin, norepinephrine, and dopamine reuptake inhibition and release</td>
<td>Deficits in spatial memory (111); mild impairment on psychomotor tasks (92)</td>
<td>Changes in body perception, slight visual and auditory alterations, no hallucinations (92)</td>
<td>Distrust and hostility (103); anxiety (93, 101, 103, 105)</td>
<td>Increased trust and sense of a greater meaning in life (100); euphoria (92, 103) and well-being (92)</td>
<td>Increased connectedness toward others (91, 99, 102); increased empathy (96, 100, 103)</td>
<td>MDA, MDEA</td>
</tr>
<tr>
<td><strong>Dissociative anesthetics</strong></td>
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</tr>
<tr>
<td>Ketamine</td>
<td>NMDA antagonist</td>
<td>Deficits in vigilance, verbal fluency, delayed recall, and tests of frontal lobe function (121)</td>
<td>Derealization, depersonalization (8, 120, 121, 124); illusions in all sensory domains and perceptual alterations (121)</td>
<td>Amotivation, emotional dulling, hostility (121); anxiety (121, 123)</td>
<td>Improved mood (7, 8, 120, 123)</td>
<td>Emotional withdrawal (121)</td>
<td>Dextromethorphan, phencyclidine (PCP), and nitrous oxide</td>
</tr>
</tbody>
</table>

*Reiff et al.*

Am J Psychiatry, 2020
Pharmacology of Human Behaviors

Phenethylamines
(MDMA, Mescaline)

Tryptamines
(Psilocybin, DMT)

Stimulants
(Cocaine, Amphetamines)

Sedatives
(Opioids, Alcohol)

adapted from Schwartz
Basic human values, 2006
Neurobiological Mechanisms

**a**

Throughput is thought ultimately to lead to increased expression of BDNF.

The increased AMPA-receptor-mediated throughput relative to NMDA-receptor-mediated signaling to enhanced firing of glutamatergic projection neurons and increased extracellular glutamate.

**b**

- **Cortical layer V**
  - NMDAR
  - AMPAR
  - Glutamate release
  - BDNF

- **Deep cortical layers**
  - 5-HT2A
  - 5-HT neuron
  - Psilocin/LSD/DMT

- **Brainstem**
  - Psilocin/LSD/DMT

**Vollenweider & Kometer**

Neurobiological Mechanisms

Brain communication patterns

placebo

psilocybin

Image courtesy of Dr. Robin Carhart-Harris
Neurobiological Mechanisms

Andrews-Hanna et al.
Neuron, 2010

SELF > CONTROL

Evoked changes were analyzed with a cluster-based approach, applying a Family Wise Error (FWE) correction for multiple comparisons. A pair-wise comparison between conditions (Self > Control) was performed using a Wilcoxon rank-sum test. The maps in Fig. 1b are corrected for multiple comparisons using a false discovery rate (FDR) correction.

Collectively, these results indicate that the Default Mode Network (DMN) was activated during self-referential processes. Psilocybin administered in a placebo condition significantly decreased post-intervention in the DMN hubs (compare to placebo).

Smigielski & Scheidegger et al.
Neuroimage, 2019

Changes in functional connectivity of the default mode network during open awareness meditation

A

B

C

$\beta = -0.17$

$\beta = -0.11$

$\beta = -0.12$

$\beta = -0.18$

$\beta = -0.16$

$\beta = -0.09$

$\beta = -0.009$

Significant clusters of increased connectivity are highlighted in yellow. Based on the statistical analysis, we observed a significant increase in connectivity between the main default mode network components: (D) Rsp, (E) TPJ, (F) pIPL, (G) LTC, and (H) TempP.

Scheidegger et al.
PloS One, 2012

Default Mode Network (PCC)

Dorsal Nexus (DMPFC)

Ketamine ↓

DMN (PACC/MPFC)

Affective Network (sgACC)

Ayahuasca (Palhano-Fontes et al. 2015)

Analysis of Component Processes

To gain insight into the component processes, we performed a series of analyses. We first identified the core components of the default network, which are known to be involved in self-reflection and introspection. We then examined the spatial distribution of activity across the network, as well as the temporal dynamics of connectivity within and between regions.

Lebedev et al., 2015

Collective efforts showed the greatest effort. Additionally, strategy probes were also examined to determine the extent to which participants engaged in reflective processes. The results indicated that participants were more likely to engage in self-reflection when solving tasks that required the use of external strategies.

Ayahuasca

Meditation and psilocybin have been shown to share common neural correlates. Ayahuasca and psilocybin intake were associated with increased functional connectivity within the default mode network. These findings suggest that both substances may induce a state of mindfulness.

Non-Self Control

The mask that defined the DMN, outlined from a control group, is shown in (see). Strategy probe question #11 asked participants to rate their experience of self-transcendence during Ayahuasca intake. The results indicated a positive correlation between self-transcendence and connectivity within the default mode network.

The Brain's Default Network

Antero-posterior DMN connectivity was also examined. A significant increase in connectivity was observed between the posterior and anterior regions of the DMN. This finding suggests that Ayahuasca intake may enhance the functional integration of the DMN.

Carhart-Harris et al., 2012

The changes in connectivity were analyzed using a group analysis approach. We performed a voxel-wise analysis of the reported strategies that tracked activity differences between conditions. A significant increase in connectivity was observed between the main default mode network components.

Johnson et al., 2002

Multivariate analysis of variance (MANOVA) was performed to compare the connectivity patterns between conditions. A significant increase in connectivity was observed between the main default mode network components.

Core areas of the DMN were strongly correlated with each other (aMPFC with mPFC). The same applied to the posterior regions of the DMN. This finding suggests that the DMN components work in concert to support self-referential processes.

Similarly, the mean correlation of 0.01). A final analysis of the reported strategies that tracked activity differences between conditions. A significant increase in connectivity was observed between the main default mode network components.

Erlacher et al., 2015

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Lebedev et al., 2015

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Neurobiological Mechanisms

Carhart-Harris and Friston
Pharmacological Reviews, 2019
Increased amygdala reactivity after psilocybin-assisted therapy predicts antidepressant effect

Roseman et al.
Neuropharmacology, 2017

Decreased amygdala reactivity following SSRI treatment

DeRubeis et al.
Nat Rev Neurosci, 2008
Neurobiological Mechanisms

Bipartite model of brain serotonin function

1) Post-synaptic 5-HT1AR-mediated passive coping • Modulated by SSRIs (chronic-use)
   - Basic action
     - Post-synaptic 5-HT1AR signalling ↑
     - Limbic responsivity ↓
   - Functions reduced
     - Stress, impulsivity, aggression, anxiety ↓
   - Functions enhanced
     - Resilience ↑
     - Patience ↑
     - Emotional blunting ↑
     - Tolerance of stress ↑

Pathway 1 (modulated by conventional antidepressants)

2) 5-HT2AR-mediated active coping • Modulated by psychedelics
   - Basic action
     - 5-HT2AR signalling ↑
     - Cortical entropy ↑
   - Functions reduced
     - Rigid thinking ↓
     - Pessimism ↓
   - Functions enhanced
     - Plasticity ↑
     - Environmental sensitivity ↑
     - Learning & unlearning ↑
     - Adaptability/change ↑

Pathway 2 (modulated by 5-HT2AR agonist psychedelics)

Depression ↓
Well-being ↑

Carhart-Harris & Nutt et al.
Therapeutic process with rapid-acting psychoactive compounds

Psychopharmacotherapy with continous learning and experiencing with improvements and relapses

Scheidegger
Info Neurologie & Psychiatrie, 2018
Stuck in a rut: rethinking depression and its treatment

Paul E. Holtzheimer and Helen S. Mayberg
Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 101 Woodruff Circle NE, Suite 4000, Atlanta, GA 30322, USA

Therapeutic process with rapid-acting psychoactive compounds

Transformational Psychotherapy

Scheidegger
Info Neurologie & Psychiatrie, 2018
Towards Rapid-acting Antidepressants

Ketamine
i.v. anaesthetic
Zarate et al.
Arch Gen Psych, 2006.

Psilocybin
"magic mushrooms"
Carhart-Harris et al.

DMT / Harmine
"ayahuasca"
Palhano-Fontes et al.

Mostly stand-alone treatment
Require psychological support (e.g. guidance, introspection, self-discovery)
## Towards Rapid-acting Antidepressants

<table>
<thead>
<tr>
<th>Properties</th>
<th>Ketamine</th>
<th>Psilocybin</th>
<th>Ayahuasca</th>
</tr>
</thead>
<tbody>
<tr>
<td>rapid antidepressant onset</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>sustainability of treatment response</td>
<td>X</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>no additive potential</td>
<td>X</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>no tolerance induction</td>
<td>X</td>
<td>X</td>
<td>✔</td>
</tr>
<tr>
<td>no acute / chronic toxicity</td>
<td>✔</td>
<td>X</td>
<td>✔</td>
</tr>
</tbody>
</table>
Ayahuasca is increasingly recognized due to its adaptogenic health effects and may be particularly well suited for the systemic treatment of complex diseases:

- **antidepressant effects**  (Palhano-Fontes et al. 2018)
- **anxiolytic effects**  (dos Santos et al. 2016)
- **anti-addictive effects**  (Liester & Pricket, 2012)
- **cognitive flexibility**  (Kuypers et al. 2016)
- **emotion regulation**  (Domínguez-Clavé et al. 2019)
- **mindfulness-related capabilities**  (Soler et al. 2016)
- **immunomodulatory effects**  (dos Santos et al. 2014)
- **neuroprotective effects**  (Szabo et al. 2016)
- **neurotrophic effects**  (Morales-Garcia et al. 2017)
“Adaptogenic herbs, also referred to as “adaptogens,” are defined as agents that support the body’s ability to accommodate varying physical and emotional stresses.”

Adaptogenic Herbs: What Are Adaptogens
Globale Expansion of Ayahuasca

Ayahuasca psychedelic tested for depression

Pilot study with shamanic brew hints at therapeutic potential.

Arran Froom

06 April 2015
The Ayahuasca Experience
The Ayahuasca Experience
„I feel more able to be with myself. I feel more capable of experiencing my emotions. So that I don’t go to those behaviors that shove those emotions down that I don’t want to experience anymore.“

(patient self-reports)
„I did notice a huge, huge change [in eating disorder symptoms]. It’s just hard to describe but I felt like I had more distance between my behaviors and, you know the thought patterns and the triggers and just felt like I didn’t need to have those coping skills anymore. [...] It was like my brain was reprogrammed. It’s the only way I can describe it - I don’t know exactly how it works.“

(patient self-report)
„Ayahuasca helped me deeply connect with myself so that self-love has been the prevalent priority over self-criticism that [...] self-love became more important and more prevalent. And that to me is the antidote for an eating disorder.“

(patient self-report)
Future Directions and Challenges

Ritual of Yagé
Colombia
Future Directions and Challenges
Transformational Consciousness Technologies

**Clinical studies about efficacy of ayahuasca-based psychotherapy for stress-related affective disorders**

**Developing a standardized botanical extract analogue to traditional ayahuasca**

**Multimodal neuroimaging of neural correlates of emotional reactivity, social cognition, and self-referential processing in healthy subjects**

**Assessing safety and tolerability including pharmacokinetics and brain dynamics (phEEG)**
Pharmacology of Ayahuasca

*N,N-Dimethyltryptamine (N,N-DMT)*
- orally inactive (degradation of GI-MAO-A)
- orally active, when combined with MAO-A inhibitors
- affinity for 5-HT1A/2A/2C, D1-3, alpha1A/2A, TAAR1, H1, SERT, DAT, NET

*Beta-Carbolines (i.e. harmine, harmaline, THH, etc.)*
- act as reversible MAO-A inhibitors
- prevent degradation of N,N-DMT and also 5-HT, NA

*Banisteriopsis Caapi*

*Psychotria Viridis*

*N,N-Dimethyltryptamine (N,N-DMT)*
- orally inactive (degradation of GI-MAO-A)
- orally active, when combined with MAO-A inhibitors
- affinity for 5-HT1A/2A/2C, D1-3, alpha1A/2A, TAAR1, H1, SERT, DAT, NET

Carbonaro et al.
Brain Res Bull, 2016
Pharmacology of Ayahuasca

Extraction of N,N-DMT from Mimosa hostilis (Incubator Lab, IREM UZH)
Study Design

*Psychedelic Lab Space @ University of Irchel*
Invited review

Positive psychology in the investigation of psychedelics and entactogens: A critical review

Henrik Jungaberle a,*, Sascha Thal b, Andrea Zeuch a, Ansgar Rougemont-Bücking c, Maximilian von Heyden d, Helena Aicher e, Milan Scheidegger e

Highlights

• 77 clinical trials and epidemiological studies with 9876 participants applied measures from positive psychology.

• Psychedelics and entactogens showed positive effects e.g. on well-being, prosocial behaviours, empathy, creativity, personality, values and mindfulness.

• Research with less biased clinical and healthy populations in prospective longitudinal designs is needed to assess sustainability, context factors and benefit-risk-ratio.
Therapeutic Change Processes

ACT-Hexaflex Model
Fig. from Prevedini et al. 2011
Therapeutic Setting

Therapeutic context for psychedelic-assisted therapy (set - setting - intention)

- **preparation sessions**
  - explore the patient's symptoms, life history, and potential for psychological growth
  - therapeutic alliance, psychoeducation, setting intentions for the dosing session

- **dosing sessions**
  - facilitation of a sense of safety, trust and openness
  - male-female co-therapy team in a comfortable room, option for listening to music

- **integration sessions**
  - interpret the content of the psychedelic experience into meaningful long-term change
  - modify maladaptive patterns of behavior, thoughts, and emotions

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**Psycholytic Therapy**

- low to moderate doses over several sessions
- access to the unconscious or repressed emotions
- discharge of emotionally charged psychic tension

**Psychedelic Therapy**

- one or several high-dose sessions
- self-transcendent or peak experience
- novel insights into the patient's condition
Therapeutic Setting

Pre-state, dose & setting → State → Longer-term outcome(s)

- **Readiness ↑**
  - $\beta = 0.16$, $p = 0.076$

- **Intention ↑**
  - $\beta = 0.26$, $p < 0.01$

- **Therapeutic setting ↑**
  - $\beta = 0.26$, $p = 0.013$

- **Drug dose ↑**
  - $\beta = 0.2$, $p = 0.04$

- **Readiness ↓**
  - $\beta = -0.46$, $p < 0.01$

- **Intention ↓**
  - $\beta = -0.25$, $p = 0.02$

- **Trust ↓**
  - $\beta = -0.37$, $p < 0.01$

**Peak Experience ↑**
- $\beta = 1.96$, $p < 0.001$

**Well-being ↑**

**Challenging Experience ↑**
- $\beta = -1.12$, $p < 0.005$

**Well-being**

Carhart-Harris et al.
J Psychopharmacol 2018
Challenging Experiences

How personally difficult or challenging was the experience?

- Single most
- Among top 5
- Among top 10
- Once every 5 years
- Once a year
- Once a month
- Once a week
- Everyday experience

Survey of psilocybin use outside of therapeutic context

Percentage of Participants

How personally meaningful was the experience?

- Single most
- Among top 5
- Among top 10
- Once every 5 years
- Once a year
- Once a month
- Once a week
- Everyday experience

Percentage of Participants

Duration of challenging experience (N = 1993)

- Entire session
- > 2 hour, not entire session
- 1 to 2 hour
- 30 to 60 minutes
- 10 to 30 minutes
- < 10 minutes
- Don’t know

Percentage of Participants

Enduring change in personal well-being or life satisfaction

- Increased very much (+3)
- Increased moderately (+2)
- Increased slightly (+1)
- No change (0)
- Decreased slightly (-1)
- Decreased moderately (-2)
- Decreased very much (-3)

Percentage of Participants

Carbonaro et al.
J Psychopharmacol 2016
Challenging Experiences

Strategies attempted and strategies that substantially helped to stop the challenging experience (N = 1993)

- Tried to calm your mind
- Changed location
- Used your body to shift the experience
- Changed music environment
- Changed social environment
- Asked for help from friend
- Smoked cannabis
- Other
- Changed environment in other ways
- Drank alcohol
- Took another drug

Survey of psilocybin use outside of therapeutic context

Percentage of Participants

Carbonaro et al.
J Psychopharmacol 2016
Nutzen, Risiken und Grenzen

Source: "Drug harms in the UK: a multicriteria decision analysis", by D. Nutt et al., The Lancet
The Economist

Nutt et al.
The Lancet 2010
Serious psychological distress
K6-scale

Mental health treatment
Inpatient
Outpatient
Medication
Needed but did not receive

Suicidal
Thought about killing self
Planned to kill self
Attempted to kill self

Depression and anxiety
Symptoms of major depressive episode
Diagnosis of depression
Diagnosis of anxiety disorder

aOR and 95% CI

Johansen and Krebs
Journal of Psychopharmacology, 2015
Nutzen, Risiken und Grenzen

Subakute halluzinogen-induzierte psychotische Störungen (ICD-10: F16.5):

- bei Patienten mit einer entsprechenden Prädisposition können latente Psychosen und Schizophrenien ausgelöst werden.
- bei remittierten Psychose-/Schizophrenie-Patienten können Rezidive mit teils persistierenden psychotischen Verläufen begünstigt werden.

Chronische Komplikationen (ICD-10: F16.7): HPPD („Flashbacks“)

- Bis zu 60 % der Konsumenten berichten einmalige oder wiederkehrende „Flashbacks“ (meist nach LSD), wobei auch deutlich tiefere Zahlen berichtet wurden.
- Ca. 4% der LSD-Konsumenten berichten nachhaltige und funktionseinschränkende „Flashbacks“.
- Nach experimentell verabreichtem LSD entwickeln 0.1% bis 4.6% der Teilnehmer eine Psychose, wobei Patienten häufiger betroffen sind, vereinzelt wurden auch Fälle von Panikstörung und PTSD meist nach „Bad Trips“ beschrieben.
- HPPD wurde am häufigsten nach Konsum LSD oder PCP, vereinzelt aber auch bei MDMA, Meskalin, Psilocybin, Ayahuasca, Ketamin, Dextromethorphan, Muscimol, Stechapfel (Datura), Salvinorin-A, Ibogain, Cannabis und synthetischen Cannabinoiden beobachtet.
Nutzen, Risiken und Grenzen

- Auf ein geeignetes **Set** (innerer Zustand) und **Setting** (Umfeld) ist aufgrund der stark kontextsensitiven Wirkung dieser Substanzen unbedingt zu achten.

- **Supportive Psychotherapie im Plastizitätsintervall** um korrektive Bewusstseinserfahrungen weiter zu stabilisieren

- **Aufklärung, Nutzen-Risiko-Analyse** und Einverständnisserklärung

- Pharmakologisch induzierte veränderte Bewusstseinszustände können aufgrund ihrer ungewohnten **Intensität** bei entsprechender **Prädisposition** akut auch **Angst, Panik oder Gefühle von Kontroll- und Realitätsverlust** auslösen.

- **Psychiatrische Kontraindikationen**: akute **Suizidalität**, emotionale **Instabilität** oder Psychoseanfälligkeit

- **Kardiales Screening und regelmässiges Monitoring** der **Vitalparameter** während der Sitzung (BD-/Pulsanstieg)

- **Medikamenteninteraktionen**: Antiglutamaterge und GABAerge Medikamente (z.B. Antiepileptika, Benzodiazepine), **Opiode** und **SSRIs** mildern die Wirkung serotonerger Psychedelika ab, während **MAO-Hemmer** zu einer unvorhersehbaren Wirkungsverstärkung beitragen und wegen der Gefahr eines **Serotoninsyndroms** daher kontraindiziert sind.
• **Toxikologisch** gelten glutamaterge und serotonerge psychoaktive Substanzen bei den im therapeutischen Rahmen üblichen Dosierungen und Behandlungsfrequenzen als hinreichend sicher.

• Im Gegensatz zu häufig verschriebenen Betäubungsmitteln wie Benzodiazepinen und Opiaten, weisen serotonerge psychoaktive Substanzen kein Risiko für eine körperliche Abhängigkeitsentwicklung auf.

• Die Lebenszeitprävalenz der Einnahme von Psychedelika ist nicht mit einem erhöhten Risiko für psychiatrischen Erkrankungen assoziiert ist.

• Das Risiko für Langzeitnebenwirkungen wird zudem durch die unregelmässige und limitierte Anzahl an Behandlungen gesenkt, was auch gesundheitsökonomische Vorteile hat.

• Da die meisten bekannten Wirkstoffe nicht patentierbar sind, steigen die Anreize für industrielle Forschung und pharmazeutische Entwicklung im Bereich von Analoga und Derivaten mit geringeren psychotropen Eigenschaften und verbessertem Risikoprofil.
Der klinisch-experimentelle Einsatz psychoaktiver Substanzen wird seit einigen Jahren wieder vermehrt wissenschaftlich untersucht.

Abhängigkeitserkrankungen, Stress- und Traumafolgestörungen sowie Angststörungen und Depression bei lebensbedrohlicher körperlicher Erkrankung stellen derzeit die am besten evaluierten Indikationen für die substanzunterstützte Psychotherapie mit serotonergen psychoaktiven Substanzen dar.

Der Behandlungsansatz mit psychoaktiven Substanzen beruht nicht auf einer längerdauernden pharmakologischen Substitution von Neurotransmittern, sondern zielt als transformationsorientiertes Paradigma auf die rasche Veränderung dysfunktionaler neuronaler Regelkreise ab.

Psychoaktive Substanzen zeigen in einem kontrollierten klinisch-experimentellen oder wissenschaftlichen Setting ein relativ gutes Sicherheitsprofil und eine gute Verträglichkeit.

Die experimentelle Behandlung mit nicht verkehrsfähigen Substanzen unterliegt der Bewilligungspflicht durch die kantonalen Ethikkommissionen sowie des BAGs und ist vorerst nur in wissenschaftlich begleiteten Kontexten oder für experimentelle individuelle Heilungsversuche möglich.
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